REMARKS

Claims 55-75 are currently pending. Claims 55, 66, and 67 have been amended herein, and new claims 76-80 have been added. Support for new claims 76 and 77 can be found on page 1 and pages 15-16, which indicate that sporocysts are contained within the walls of sporulated oocysts, and that sporulated oocysts can be treated to disrupt the oocyst wall and release sporocysts. Support for the amendment to claim 67 can be found on page 15, which indicates that sporulated oocysts (i.e. "coccidial protozoa") may be washed by tangential flow filtration, and on page 16, lines 25-26, which indicate that the sporocysts may be washed following sanitation. Claim 55 has been amended to more accurately reflect a preferred embodiment of the invention, by indicating that the coccidial protozoa are sanitized, and that oocysts containing the live sporocysts have been separated by tangential flow filtration from an aqueous composition containing bacterial or fungal contaminants. Support for this amendment can be found on page 15, which discloses that sporulated oocysts can be filtered by tangential flow filtration after disinfection. Claim 66 has been amended to better define another preferred embodiment in which the sporocysts have been released from sporulated oocysts of at least one species of coccidial protozoa, and thereafter sanitized. Support for this amendment can be found on pages 15-16. The phrase "wherein said at least one species of coccidial protozoa comprises *Eimeria tenella, Eimeria maxima,* and *Eimeria acervulina*" has been removed from claim 66, and now forms the basis of new dependent claim 78.

Objections to the Specification

The Office has maintained the objection to page 21 of the specification, stating that page 21 still contains embedded hyperlinks. Applicants respectfully direct the Office's attention to the amendments made to the specification in Amendment B, filed May 5, 2003, which removed the hyperlink from page 21 of the specification. If further objectionable material appears on page 21, applicants respectfully ask that the Office specifically point out the line on page 21 which contains such material.

Rejection under 35 U.S.C. § 102(b)

The Office has rejected claims 55-60 and 66-70 under 35 U.S.C. § 102(b) as being anticipated by Evans, et al. (WO 96/40233).

Claims 55-65, and new claims 76 and 77 are directed to preparations for the prevention and treatment of coccidiosis in members of the class *Aves* comprising live sporocysts of at least one species of coccidial protozoa, and a pharmaceutically acceptable carrier, diluent, or excipient. The coccidial protozoa have been sanitized, and oocysts containing the live sporocysts have been separated by tangential flow filtration from an aqueous composition containing bacterial or fungal contaminants.

Claims 66-75, and new claims 78-80 are directed to preparations for the prevention and treatment of coccidiosis in members of the class *Aves* comprising live sporocysts of at least one species of coccidial protozoa, and a pharmaceutically acceptable carrier, diluent, or excipient. The sporocysts have been released from sporulated oocysts of said at least one species, and thereafter sanitized.

Evans, et al. disclose a method for the *in ovo* vaccination of domesticated birds against coccidiosis using live *Eimeria* sporocysts, oocysts, or a mixture thereof. Evans, et al. further disclose a preferred dose of from 10^2 to 10^8 sporocysts per egg,[1] and indicate that such sporocysts or oocysts may be from two or more species of *Eimeria*, including the species *E. tenella, E. acervulina, E. maxima, E. necatrix, E. mitis, E. praecox,* and *E. brunetti*, among others. The use of suspending agents and immune stimulants in combination with the vaccine compositions is also disclosed.

In order to anticipate a claim, every element of the claim must be described, either expressly or inherently, in a single reference.[2] Contrary to the Office's assertion, Evans et al. do not "teach all the limitations of the instant claims."

The Office has stated that "[t]he purification or production of a product by a particular process (i.e. the tangential flow filtration) does not impart novelty or

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[1] WO 96/40233 (Evans, et al.), p. 6, ln. 25-30.

[2] *See* MPEP §2131.

unobviousness to a product when the product is taught by the prior art." Applicants respectfully submit that the preparations of claims 55-60 and 76-77 are not taught by Evans, et al.

Amended claim 55 provides that oocysts containing the live sporocysts have been separated by tangential flow filtration from an aqueous composition containing bacterial or fungal contaminants. The specification discloses that tangential flow filtration may be used after flotation to remove residual sugar,[3] and after sanitation of the oocysts with a disinfectant (e.g. sodium hypochlorite).[4] The contaminants referred to in claim 55 may thus include non-viable contaminants (e.g. contaminants killed as a result of exposure to a disinfectant), as well as viable contaminants. Tangential flow filtration allows the oocysts to be separated from non-viable contaminants.[5] Because the oocysts of claim 55 are separated from the aqueous composition by tangential flow filtration, fewer viable *and* non-viable contaminants are present in the final preparation than would be were the oocysts not separated by tangential flow filtration from a contaminant-containing aqueous composition.

In contrast, Evans, et al. fail to disclose the separation of oocysts containing live sporocysts from an aqueous composition containing bacterial or fungal contaminants by tangential flow filtration. In Evans, et al., the sporulated oocyst suspension from which sporocysts are obtained is incubated in sodium hypochlorite, which is subsequently removed by repeated washings. While sanitation with sodium hypochlorite may kill at least a portion of viable contaminants, sanitation with sodium hypochlorite does not remove non-viable contaminants from a suspension. Evans, et al. state that repeated washing of the oocysts "involves collection of oocysts by centrifugation and

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[3] Specification, p. 14, ln. 10-11.

[4] *Id.* at p. 15, ln. 13-14.

[5] "[T]he residual sugar can be removed by filtration using filters with a pore size which excludes the oocysts. When filtration is used, tangential flow is preferred." *Id.*, p. 14, ln. 10-11.

resuspending in deionized or distilled water."[6] However, such repeated washing cannot be said to inherently separate the oocysts from non-viable contaminants. Thus, when the oocysts are resuspended, some of the non-viable contaminants may remain in the suspension, and may ultimately be present in the final sporocyst-containing composition. The presence of non-viable contaminants in the final composition may result in a pyrogenic reaction in animals to which the composition is administered. In contrast, the risk of a pyrogenic reaction occurring may be reduced by removing some of the non-viable contaminants, such as by tangential flow filtration.

Given the foregoing, applicants respectfully submit that the preparation of claims 55-60 and 76-77 are not described by Evans, et al.

With regards to the term "sanitized," the Office has stated that "the composition of live sporocytes described by Evans et al, inherently and necessarily meet this recited property," since "the sporocysts of Evans were prepared by substantially the same method as described in this specification." Applicants respectfully submit that the preparations of claims 66-70 and 78-80 are not described by Evans, et al.

The specification of the present invention discloses that released sporocysts may optionally be obtained by treating sporulated oocysts to disrupt the oocyst wall.[7] Following such treatment:

> the coccidial parasites are sanitized by any suitable method. Any method that results in the destruction of microbial contaminants, but does not significantly decrease the viability of the coccidial parasites can be used. Generally, sanitation is accomplished by the use of a chemical disinfectant. In one embodiment, sanitation is by suspension in sodium hypochlorite followed by washing with sterile water as described above.[8]

Thus, in this embodiment, the sporocysts are sanitized following their release from the sporulated oocysts.

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[6] WO 96/40233 (Evans, et al.), p. 6, ln. 13-15.

[7] Specification, p. 15-16.

[8] *Id.* at p. 16, ln. 21-26.

The Evans, et al., vaccine is not prepared in this manner. In preparation of the Evans, et al. vaccine, only the precursor sporulated oocysts are contacted with a disinfectant (e.g. incubation in sodium hypochlorite), and the disinfectant is then removed by repeated washings.[9] Only after the disinfectant has been removed are the sporulated oocysts of Evans, et al., broken to release sporocysts.[10] Evans, et al., disclose that breaking of oocysts may occur "by mixing the oocysts with glass beads of 1-4 mm diameter and shaking by hand, vortex mixer, or shaking incubator, or using a hand-held homogenizer."[11] The released sporocysts may then be isolated from unbroken oocysts and oocyst walls by differential centrifugation, and used in the claimed vaccination method.

Because Evans, et al., do not sanitize the sporocyst suspension following the breaking of the oocysts, any contamination introduced into the suspension during this process will be present in the final composition. In contrast, the sporocysts in the preparations of claims 66-70 and 78-80 are sanitized following the release of the sporocysts from the sporulated oocysts. As a result, any contaminants introduced into these claimed preparations during the disruption of the oocysts are subjected to sanitation. The composition of Evans, et al., is thus not prepared by the same method as the preparations of claims 66-70 and 78-80.

Evans, et al., effectively teach away from sanitizing sporocysts that have been released from the sporulated oocysts. Evans, et al., describe in detail the preparation of the sporocysts, including the sanitation of the precursor oocyst suspension, careful removal of the disinfectant (sodium hypochlorite) by repeated washings, and the breaking of the oocysts to release the sporocysts. In contrast to the express

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[9] WO 96/40233 (Evans, et al.), p. 6, ln. 12-18.

[10] *Id.* at ln. 12-30.

[11] *Id.* at ln. 21-22.

requirements of amended claims 66-70, and new claims 78-80, Evans, et al., entirely omit a step comprising sanitizing the released sporocysts.

Given the foregoing, applicants respectfully submit that claims 66-70 and new claims 78-80 are not described by Evans, et al.

Claims 58 and 80 are directed to preparations comprising coccidial protozoa of the species *Eimeria tenella, Eimeria maxima,* and *Eimeria acervulina*. Evans, et al., disclose that the sporocysts or oocysts used therein may be of two or more species of *Eimeria* selected from the group consisting of *E. tenella, E. acervulina, E. maxima, E. necatrix, E. mitis, E. praecox,* and *E. brunetti*, among others. The number of combinations of two or three different species that may be drawn from the Evans list is large. Applicants' attorneys calculate the combinations of two or three out of a population of seven protozoan species to be in excess of 50, or more precisely 56. While Applicants do not wish to be held to the accuracy of that computation, the combinations are clearly too numerous for the selection of *E. tenella, E. acervulina*, and *E. maxima* to be rendered obvious from the list of seven. Moreover, the Evans specification is devoid of any examples or general teaching that would lead to the selection of any particular combinations of *Eimeria* species. It is, therefore, respectfully submitted that, Evans, et al. fail to suggest the specific combination of *E. tenella, E. maxima*, and *E. acervulina*, as specified in claims 58 and 80. Consequently, claims 58 and 80 are not anticipated by Evans, et al., for this additional reason.

Rejection under 35 U.S.C. § 103(a)

The Office has rejected claims 61, 62, 64, 71, 72, and 74 under 35 U.S.C. § 103(a) as being unpatentable over Evans, et al. (WO 96/40233) in view of MacDonald, et al. (U.S. Patent No. 5,055,292).

For a combination of references to render obvious a claimed invention, the Office must show: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the

reference or to combine reference teachings; (2) a reasonable expectation of success; and (3) that the prior art reference (or references when combined) teach or suggest all the claim limitations.[12] Applicants respectfully submit that this showing has not been made.

The Office has stated that Evans et al. differs from the current claims in that the addition of preservatives to the vaccine composition is not taught. The Office further states that MacDonald teaches "that it is desirable to add preservatives to vaccines to inhibit contamination with other organisms," and that it would thus be *prima facie* obvious to add a preservative according to MacDonald, et al. to the *in ovo* vaccine composition of Evans, et al.

As previously discussed, Evans, et al., unlike claims 61, 62, and 64, do not describe the separation of oocysts containing live sporocysts by tangential flow filtration from an aqueous composition containing bacterial or fungal contaminants, but rather, describe the removal of a disinfectant (sodium hypochlorite) from oocysts by repeated washings. Consequently, non-viable contaminants may remain in the oocyst suspension, and may ultimately be present in the final sporocyst-containing composition to a greater extent than found in the preparations of claims 61, 62, and 64. Furthermore, Evans, et al., do not describe the sanitation of sporocysts following their release from the sporulated oocysts, as is required for the embodiment as defined by claims 71, 72, and 74. As previously discussed, Evans, et al., actually teach away from sanitizing sporocysts released from sporulated oocysts. The compositions of Evans, et al., thus do not comprise released sporocysts that have been "sanitized."

In addition, as previously indicated, Evans, et al. do not disclose or suggest the particular combination of *E. tenella, E. maxima,* and *E. acervulina*, as called for in claims 58 and 80.

MacDonald, et al. disclose a vaccine containing live sporulated oocysts, and disclose the combination of *E. tenella, E. maxima,* and *E. acervulina*. MacDonald, et

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[12] MPEP § 2142.

al., also indicate that oocysts may be sporulated in an aqueous solution of an oxidant (e.g. potassium dichromate), which may be removed after sporulation by centrifugation.[13] MacDonald, et al., also indicate that oocysts may be treated with an antibacterial substance (e.g. sodium hypochlorite) after sporulation "to avoid contamination by other microorganisms," and may then be resuspended in water, with formalin added.[14]

MacDonald, et al. do not describe the removal of oocysts containing live sporocysts by tangential flow filtration from an aqueous composition containing bacterial or fungal contaminants. As previously discussed with regards to Evans, et al., centrifuging and resuspending oocysts does not inherently separate oocysts from non-viable contaminants. Thus, when the oocysts are resuspended, some of the non-viable contaminants may remain in the suspension, and may ultimately be present in the final composition. Thus, neither MacDonald, et al., nor the combination of Evans, et al., and MacDonald, et al., teach or suggest a preparation in which oocysts containing live sporocysts have been separated by tangential flow filtration from an aqueous composition containing bacterial or fungal contaminants, as is called for in claims 61, 62, and 64.

In addition, MacDonald, et al. do not describe the preparation or sanitation of released sporocysts as called for in the embodiment of claims 66-75 and 78-80; there is no indication that sporocysts are released from the oocysts. Any sporocysts within the suspension described in Example 1 of MacDonald are contained within the oocyst wall. Thus, the combination of Evans, et al., and MacDonald, et al. does not describe or suggest a preparation comprising released sporocysts that have been sanitized, as are called for in claims 71, 72, and 74.

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[13] U.S. Patent No. 5,055,292 (MacDonald, et al.), c. 9, ln. 16-19; c. 8, ln. 18-24.

[14] *Id.* at c.8, ln. 25-28; c. 9, ln. 20-23.

Based on the foregoing, Applicants respectfully submit that claims 61, 62, 64, 71, 72, and 74 are patentable over Evans, et al. in view of MacDonald, et al.

The Office has also rejected claims 63, 65, 73, and 75 under 35 U.S.C. § 103(a) as being unpatentable over Evans, et al. (WO 96/40233) and MacDonald, et al. (U.S. Patent No. 5,055,292), as applied to claims 61, 62, 64, 71, 72, and 74 above, and further in view of Thaxton (U.S. Patent No. 5,311,841).

Thaxton, et al. is cited by the Office for disclosing the delivery of medicaments, such as other vaccines, nutrients, antibiotics (such as gentamicin), etc. to newly hatched poultry via intra-yolk sac injection.[15] Thaxton, et al. do not, however, describe the use of tangential flow filtration to separate oocysts containing live sporocysts from an aqueous composition containing bacterial or fungal contaminants, as specified in claims 55-65, 76, and 77, nor do Thaxton, et al. describe the sanitization of released sporocysts, as called for in claims 66-75 and 78-80.

As previously discussed, the combination of Evans, et al. and MacDonald, et al. does not teach or suggest each claim limitation, and in particular does not describe preparations comprising live sporocysts in which oocysts containing live sporocysts have been separated by tangential flow filtration from an aqueous composition containing bacterial or fungal contaminants, as is called for in claims 63 and 65, and preparations comprising released sporocysts that have been sanitized, as is called for in claims 73 and 75.

Example 6 of Thaxton, et al., describes the preparation of *sporozoites* by rupturing oocysts to release sporozoites and suspending the resulting sporozoites in Hanks balanced salt solution.[16] However, there is no suggestion of using tangential flow filtration to separate the precursor oocysts from a composition containing bacterial and fungal contaminants, and no disclosure or suggestion that the released sporozoites

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[15] U.S. Patent No. 5,311,841 (Thaxton, et al.), c. 3-4.

[16] *Id.*, at c. 21, ln. 2-12.

be sanitized. Furthermore, there is no description of the release, or sanitation, of released sporocysts.

Thus, the combination of Evans, et al., and MacDonald, et al., and Thaxton, et al., does not teach or suggest each claim limitation of claims 63, 65, 73, and 75.

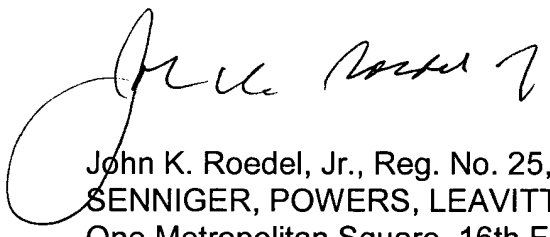
Based on the foregoing, applicants respectfully submit that claims 63, 65, 73, and 75 are patentable over Evans, et al. and MacDonald, et al., in further view of Thaxton, et al.

CONCLUSION

In light of the foregoing, applicants submit that claims 55-80 are in proper form for allowance, and respectfully request favorable consideration of the application.

The Commissioner is hereby authorized to charge any underpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,



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